

REMARKS

A. Status of the Claims

Claims 1, 21 and 24 are cancelled, claim 42 is added, and claims 2, 6, 11, 16, 18, 22 and 23 are amended. Therefore, claims 2-20, 22, 23 and 42 are pending in the application with entry of this amendment. Claims 1-14 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Keogh *et al.*, Kim *et al.*, McIlroy *et al.*, or Pfirman *et al.* Claims 1-24 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Kim *et al.* in view of McIlroy *et al.*

B. Support for the Amendments

Support for the amendments to the claims can be found throughout the specification, the drawings, and the claims as originally drafted. Claim 42 has been added to more clearly recite the subject matter of Applicants' invention. Support for claim 42 is found in the specification, for example, on page 6, line 20 to page 8, line 25.

C. Rejection under 35 U.S.C. §102(b)

Claims 1-14 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Keogh *et al.*, Kim *et al.*, McIlroy *et al.*, or Pfirman *et al.* The Examiner asserts that Keogh *et al.*, Kim *et al.*, McIlroy *et al.*, and Pfirman *et al.* all teach oxidative fixation of collagenous tissue.

Applicants respectfully disagree. The Federal Circuit has held that "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." See MPEP § 2131 (quoting *Verdegal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987)).

New claim 42 recites that the biological tissue is contacted with "a solution comprising a chemical fixative agent while providing an oxidizing condition." Applicants respectfully submit that none of the cited references describe contacting a biological tissue with a chemical fixative agent while providing an oxidizing condition.

Keogh *et al.* do not even teach or suggest contacting a biological tissue with a chemical fixative agent. Keogh *et al.* teach a method for immobilizing a biomolecule coating

on the surface of a medical device, wherein a 2-aminoalcohol moiety is oxidized to a reactive aldehyde. Furthermore, Keogh *et al.* explicitly teach away from the use of a chemical fixative agent by stating: "the methods of the present invention eliminates the need for using glutaraldehyde . . . ." See column 6, lines 23-28. Because Keogh *et al.* do not disclose the use of a chemical fixative agent, Keogh *et al.* fail to meet Applicants claim element reciting "contacting said biological tissue with a solution comprising a chemical fixative agent while providing an oxidizing condition."

Kim *et al.* teach a method for the preparation of bioprosthetic heart valves resistant to calcification that involves covalently binding an anionic hydrophilic polymer derivative of sulfonated polyethylene oxide to the tissue by means of chemically modified procedures. See, Kim *et al.*, col. 3, lines 20-27. Kim *et al.* teach modifying the bioprosthetic valve by oxidation with sodium metaperiodate, neutralization with ethylene glycol, and fixation with glutaraldehyde. The oxidation and fixation procedures are separated by an intermediate neutralization step, wherein the tissue is contacted with a solution containing ethylene glycol (see *Id.* lines 35-43 and Examples 2, 3, 8, and 9). Because of this neutralization step, Kim *et al.* do not disclose treatment of tissue with glutaraldehyde while providing an oxidizing condition.

McIlroy *et al.* teach a method of tanning biomaterial to increase calcification resistance. The method involves the steps of: (1) fixing the tissue with glutaraldehyde; (2) removing the glutaraldehyde with extensive washing with saline or aqueous 50% ethanol solution; and (3) photooxidizing the tanned tissue (see Example 1). Throughout the specification, McIlroy *et al.* stress that the photooxidation step is separate from the glutaraldehyde step. In fact, McIlroy *et al.* teach that the photooxidation step and the glutaraldehyde fixation step should be performed in a specific order. For example, at column 3, lines 60-65, the specification states:

Surprisingly, biomaterial fixated by glutaraldehyde methods, and then later fixated by photooxidation, has the lower calcification potential more similar to photooxidized-only fixated biomaterial, and has mechanical properties more similar to glutaraldehyde-only fixated biomaterial.

From the above passage, one of skill would understand not only that glutaraldehyde treatment should be separate from oxidation, but that the order of glutaraldehyde and

oxidation treatment is important. Because McIlroy *et al.* teach that oxidation and fixation should be performed separately and in a specific order, McIlroy *et al.* fail to teach or suggest the treatment of tissue with a chemical fixative agent while providing an oxidizing condition.

Pfirman *et al.* teach a method for treating bacterially infected bone cavities with an implant containing crosslinked collagen. Notably, Pfirman *et al.* teach treatment of collagen that has been isolated from biological tissue but do not teach chemical fixation or oxidation of biological tissue. Even as to collagen treatment, Pfirman *et al.* either teach oxidation of collagen fibers (to artificially age them) or cross-linking collagen fibers with an aldehyde such as glutaraldehyde. Thus, far from suggesting or teaching chemical fixation of biological tissue while providing an oxidizing condition, Pfirman *et al.* do not even disclose oxidation and aldehyde treatment of collagen fibers in successive steps (see column 2, lines 33-51).

Because none of the cited references describe treatment of tissue with a chemical fixative agent while providing an oxidizing condition, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102(b).

D. Response to Claim Rejections Under 35 U.S.C. §103(a)

Claims 1-24 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Kim *et al.* in view of McIlroy *et al.* The Examiner asserts that Kim *et al.* and McIlroy *et al.*, alone or in combination, teach oxidative fixation of collagenous tissue.

As an initial matter, Applicants have canceled claim 1 and added new claim 42. New claim 42 recites concurrent oxidation and chemical fixation. None of the cited references teach or suggest concurrent oxidation and chemical fixation in accordance with claim 42 as discussed above. Additionally, the cited references cannot be modified or combined to make the invention of claim 42 obvious as discussed more fully below.

**Burden of procedure.** "The examiner bears the burden of establishing a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Only if this burden is met does the burden of coming forward with rebuttal arguments or evidence shift to the applicant. *Rijckaert*, 9 F.3d at 1532, 28 USPQ2d at 1956. When the references cited by the examiner fail to establish a *prima facie* case of obviousness, the

rejection is improper and will be overturned. *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988)." See *In re Deuel*, 51 F.3d 1552, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995).

***Prima facie* obviousness requires a specific motivation to combine references.** "To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)." See MPEP 2142.

**No specific motivation to make the claimed combination has been provided.** Case law requires that the Examiner provide a specific motivation in the art for combining known elements in order to establish obviousness of the combination.

"[C]ase law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references . . . Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight . . . [Evidence of a suggestion, teaching, or motivation to combine] must be clear and particular . . . Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence' . . . [A] reference-by-reference, limitation-by-limitation analysis fails to demonstrate how the [cited] references teach or suggest their combination . . . to yield the claimed invention," and a conclusion of obviousness based on such an analysis "as a matter of law, cannot stand." *In re Dembiczak*, 175 F.3d 994, 999, 1000, 50 USPQ2d 1614, 1617, 1618 (Fed. Cir. 1999).

The Examiner has provided no clear, particular suggestion or motivation in the cited prior art to make the *specific* combination of concurrent chemical fixation and oxidation recited in the pending claims. In fact, there is no suggestion or motivation in Kim

*et al.* or McIlroy *et al.* to modify or combine the teachings disclosed therein. Kim *et al.* does not suggest that there is any deficiency in the disclosed methods that could be remedied by excluding the intermediate neutralization step and combining the oxidation and fixation steps. Similarly, McIlroy *et al.* does not suggest that there is any deficiency in the disclosed methods that could be remedied by excluding the extensive washing steps and combining the oxidation and fixation steps.

Furthermore, the cited prior art teaches against its combination or modification to obtain Applicants' invention. For example, after reviewing McIlroy *et al.*, one of skill in the art would not expect to successfully treat biological tissue with a fixative agent while providing oxidative conditions. As discussed above, McIlroy *et al.* teach a very precise sequence of steps, i.e., the photooxidation step should be performed after the glutaraldehyde fixation step rather than before (see column 3, lines 60-65). Such insistence on the specificity of the sequence of steps clearly teaches away from combining the steps.

In the absence of a specific suggestion or motivation to combine or modify the prior art, a rejection under section 103 is based merely on hindsight in light of Applicants' disclosure. *Prima facie* obviousness has not been established under such conditions, and a rejection based on such an unmotivated combination of references will not stand as a matter of law.

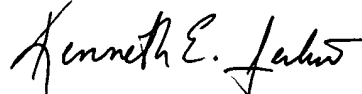
Therefore, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103(a).

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. A Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

If an appropriate payment does not accompany or precede this submission, the Commissioner is hereby authorized to charge any required fees, such as under 37 C.F.R. §§ 1.16 or 1.17, including any petition for extension of time, or to credit any overpayment, to Deposit Account No. 50-1225.

Respectfully submitted,



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